REMARKS

Claims 84, 85, 89-93 and 95-114 are pending following the amendment submitted herein. Claims 84, 95, 103 and 104 have been amended, and Claims 105-114 added. The marked up version of the claim amendments is attached hereto and is captioned "Version with Markings to Show Changes Made."

The claims stand rejected on various grounds, which will be discussed below in the order raised in the outstanding office action.

I. Interview Summary.

Applicants wish to express their appreciation for the time and courtesy extended by the Examiner toward Applicants' representative, Karen Magri, during the telephonic interview of 6 January 2003 in connection with this application. During the interview, the indefiniteness and enablement rejections were discussed as well as the possible submission of an additional Declaration under 37 C.F.R. § 1.132.

II. Support for Amendments to the Claim Set.

Written support for the amendments to Claims 84, 95, 103 and 104 and for new Claims 105-114 is discussed below.

Independent Claims 84, 95, 103 and 104 have been amended to recite "wherein said alphavirus/VEE particles infect antigen-presenting cells." Support for this amendment is found throughout the specification, including page 8, lines 16-19, which recite: "While not wishing to be held to any particular theory of the invention, it appears that the strong immunogenic response elicited in response to alphavirus, more particularly VEE, vectors is a result of alphavirus infection of dendritic cells, (*i.e.*, antigen-presenting cells)."

In addition, the claims have been amended to provide a more concise recitation of the claimed subject matter, without altering the scope of the claims.

Claims 103 and 104 have been amended to recite a "Her2 gene product" as recited in the specification.

Claim 103 has further been amended to delete extraneous words introduced into the clean version of the previous amendment.

Finally, Applicants note that an amendment introduced to Claims 84 and 95 on September 28, 2001 to recite "said composition effective to treat a cancer cell expressing said native cancer antigen" was not carried over to the previous amendment of March 26, 2002. Applicants apologize for this inadvertent error, and are deleting this language from Claims 84 and 95 in the amendment presented herein to clarify the written record for this application.

New independent Claims 105 and 110 are similar to Claims 84 and 103, except that they do not recite attenuating mutations (see dependent Claims 107 and 112) and they specifically recite that the alphavirus particles are alphavirus "replicon" particles.

Applicants submit that the amendments to the claims and the new claims are supported by the application as filed and respectfully request entry thereof.

III. Objection to Claims 103 and 104.

Claims 103 and 104 stand objected to for reciting "a Her2/neu gene product", whereas the Office Action states that the specification only provides a proper antecedent basis for reciting a "Her2" gene product. The Applicants respectfully disagree with this objection and note that it is well-settled that *ipsis verbis* support is not required in the specification. The "Her2/neu" designation is synonymous with "Her2", but the former has become the preferred designation in the scientific literature, so these two terms can be used interchangeably. The Her2 gene is the human homolog of the rat neu gene. Nonetheless, to progress the prosecution, Claims 103 and 104 have

been amended to recite "a Her2 gene product." Accordingly, Applicants respectfully request that this claim objection be withdrawn.

IV. Objection to Claim 95.

Claim 95 stands objected to for a typographical error that was introduced into the clean version of the previously amended claim. Applicants apologize for this error and appreciate the Examiner's careful reading of the claims. Claim 95 has been amended to delete the excess words, and Applicants therefore respectfully request that the objection to Claim 95 be withdrawn.

V. Enablement.

Claims 84, 85, 90-93 and 95-104 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner stating that:

> While the applicant has shown that embodiments of the viral vaccine that comprise antigens from other than the recipient are likely to be operative, no evidence has been presented to show that cancer cell antigens derived from the recipient of the vaccine are likely to be effective.. . . As most immune systems are able to distinguish between self and foreign entities, and as the applicant has not shown that the methods disclosed would be effective where the antigens are native to the recipient of the vaccine, the applicant (sic) is not enabled for embodiments where the antigen is such an antigen.

(Office Action, page 4, lines 1-11).

During the telephone interview of 6 January 2003, Applicants requested clarification of this rejection. It is Applicants' understanding that the outstanding rejection is based on the position that the data presented in the Olmsted Declaration submitted on 26 July 2001 does not establish that the present invention can be practiced to induce an immune response to a self antigen, as opposed to a foreign antigen, as it has not been clearly demonstrated that the methods of the present invention will be able to

overcome tolerance to self antigens. In particular, it is Applicants' understanding that the Examiner's concerns are based on the argument that the data in the Olmsted Declaration demonstrate vaccination of mice with an alphaviral vector expressing the rat neu gene, which would be recognized as foreign by the host mice. These issues are addressed below.

Applicants are submitting herewith an abstract and poster by Long et al., presented at the third Era of Hope meeting for the Department of Defense (DOD) Breast Cancer Research Program (BCRP) held September 25-28, 2002 at the Orange County Convention Center in Orlando, Florida. Applicants apologize for the small size of the font in this document. The studies presented by Long et al. demonstrate protection of mice transgenic for the rat neu gene following vaccination with VEE replicon particles encoding the rat neu gene product. In these transgenic animals, 50% of females develop focal mammary tumors surrounded by hyperblastic mammary epithelium by 30 weeks of age ("Introduction" of Long et al. poster). Of these animals, 70% show a tendency toward pulmonary metastatis by 8 months ("Introduction" of Long et al. poster).

Long et al. developed a tumor cell line expressing the rat neu gene. Transgenic neu expressing mice, but not wild type mice, are permissive for growth of this cell line. Vaccination of mice transgenic for the rat neu gene with a VEE replicon particle encoding a truncated version of neu (spanning the extracellular and transmembrane regions) significantly delayed or even prevented engraftment of the tumor cells (*see*, "Conclusions" section of poster). Long et al. concludes: "We believe a genetic vaccine approach using VEE replicons to target DC will result in an effective prophylactic for slowing the progression of established tumors and provide long-term protection from tumor recurrence."

Further, additional data are presented in a Supplemental Declaration of Robert A. Olmsted under 37 C.F.R. §1.132 (*hereinafter*, "Supplemental Olmsted Declaration"; to be submitted shortly hereafter) which support the enablement of the present claims. The studies in the Supplemental Olmsted

Declaration use transgenic mice that have been genetically engineered to express the rat neu gene under the control of the mouse mammary tumor virus (MMTV) promoter (known as OncoMouse, available from Charles River Laboratories). These transgenic mice spontaneously develop neu+ breast tumors 125 days after birth, which are generally lethal. Groups of ten mice were vaccinated three times with 1x 10^6 VEE replicon particles expressing the rat *neu* gene (VRP-*neu*) or an equivalent dose of control VEE replicon particles expressing influenza HA antigen (VRP-HA) on days 50, 70 and 90 post-birth.

All ten mice vaccinated with the control VEE-HA replicon particles developed tumors in most breasts between 125-200 days post-birth, and all were sacrificed due to morbidity. In stark contrast, vaccination with VRP-*neu* provided complete protection to the mice from detectable tumor formation. All mice were free of any clinical tumor development. These mice were followed to 250 days post-birth, during which time tumor-free status was maintained in all animals.

These data demonstrate that alphavirus replicon particles expressing a self antigen were able to overcome tolerance in a transgenic animal model that is considered state-of-the-art in the tumor field.

Thus, the Long et al. poster/abstract and the data provided in the Supplemental Olmsted Declaration are evidence that the alphavirus vectors of the present invention can "break tolerance" in a breast cancer model that is widely accepted in the field as among the most relevant animal models currently available. The mice described in both of these studies are transgenic for the rat *neu* gene, and thus this tumor antigen is regarded as "self" in these animals.

Accordingly, in view of the foregoing, Applicants respectfully submit that the present claims are enabled, and respectfully request withdrawal of the rejection on this basis.

VI. **Rejection under 35 U.S.C. § 112, second paragraph.**

Claims 90-93 and 95-102 stand rejected under 35 U.S.C. § 112, second paragraph for indefiniteness, the Office Action stating that the previous rejection on the basis that the claim language "native cancer cell antigen" is vague has been maintained. The Office Action states that this phrase has two possible meanings, and that Applicants' previous response did not clarify which meaning of this language was intended.

It appears that Applicants' previous response on this point was not sufficiently clear, and Applicants apologize for any confusion. The section on page 9 of the specification cited in the previous Office Action refers to an embodiment of the invention that is not presently claimed. Likewise, the cited statement from Applicants' previous response was referring to this distinct embodiment involving an artificial antigen. This portion of the specification on page 9 and these comments are not relevant to the present claims.

A native cancer cell antigen is as stated in the specification as any "naturally-occurring" cancer antigen (page 7, line 6 and at page 17, line 31) or any antigenically similar molecule. The native cancer cell antigen may be any antigen that is naturally occurring in cancer cells. The antigen need not be derived from the subject's own cancer cells, although it may be. Further, in the case of a transgenic animal, the native cancer antigen may be introduced by genetic engineering techniques.

In order for a vaccine to work, the cancer cells in the recipient will have to have an antigenically similar protein as that provided by the vaccine, but the vaccine does not necessarily have to be developed from the subject. Further, in the case of a prophylactic, the subject will not have developed cancer yet, and will not express the native cancer antigen.

In sum, a "native cancer antigen" is any naturally-occurring cancer antigen, or antigenically similar molecule. In particular embodiments, the native cancer cell antigen expressed by the alphavirus vector may be derived from the subject's own cancer. Applicants submit that this embodiment is

encompassed by the broader definition of a native cancer cell antigen as a "naturally occurring" cancer antigen.

Applicants submit that this claim language is sufficiently clear in view of the specification and the foregoing discussion, and respectfully request that the outstanding indefiniteness rejection be withdrawn.

VII. The Claims are Novel over Dubensky et al.

Claims 84, 85, 92, 93, 95, 96, 98, 100 and 102 stand newly rejected under 35 U.S.C. § 102(e) as anticipated by U.S. 5,843,723 (Dubensky et al.). Applicants respectfully traverse this rejection below.

Dubensky et al. do not disclose each and every feature of the recited claims. For example, Claims 84, 85, 92, 93, 95, 96, 98, 100 and 102 all recite that the "alphavirus particles comprise one or more attenuating mutations." Alphavirus particles comprising attenuating mutations as defined by the present invention are not disclosed or suggested by Dubensky et al.

The present application defines an "attenuating mutation" as follows:

> Preferred are alphaviruses including attenuating mutations. The phrases "attenuating mutation" and "attenuating amino acid," as used herein, mean a nucleotide sequence containing a mutation, or an amino acid encoded by a nucleotide sequence containing a mutation, which mutation results in a decreased probability of causing disease in its host (*i.e.*, a loss of virulence), in accordance with standard terminology in the art, whether the mutation be a substitution mutation or an in-frame deletion mutation. *See, e.g.*, B. Davis et al., MICROBIOLOGY 132 (3d ed. 1980). The phrase "attenuating mutation" excludes mutations or combinations of mutations which would be lethal to the virus.

(Specification; page 19, lines 14-22; emphasis added).

The Office Action states that Dubensky "teaches that the viruses may be modified such that the viral transcription of the region of the virus encoding the structural protein is not transcribed (therefore the virus is attenuated)" (Office Action, page 7). Applicants respectfully disagree. As defined by the present application, an attenuating mutation "excludes mutations or combinations of

mutations which would be lethal to the virus." Thus, deletion of entire structural protein coding regions is not an attenuating mutation in that it would be lethal to the virus, *i.e.*, prevent viral replication and propagation. Moreover, deletion of the structural protein coding regions would not be considered an "attenuating mutation" as that term is generally understood by one skilled in the art as a mutation that decreases (*i.e.*, attenuates) the pathogenicity or virulence of the virus, but does not kill the virus.

Moreover, all of the claims, including new Claims 105-114, recite that "said alphavirus particles infect antigen-presenting cells." Dubensky et al. does not disclose or suggest targeting a composition comprising alphavirus particles expressing a native cancer antigen to antigen-presenting cells (*e.g.*, dendritic cells).

Accordingly, Applicants submit that the claimed invention is novel over Dubensky et al. and respectfully request that the rejection on this basis be withdrawn.

VIII. <u>The Subject Matter of the Claims is Nonobvious over the Cited Art</u>.

Claims 84, 85, 90-93 and 95-104 stand rejected under 35 U.S.C. § 103(a) as unpatentable either over (1) WO 95/32733 (Johnston 1) in view of U.S. 5,951,975 (Falo et al.) in view of US 5,792,462 (Johnston 2) and U.S. 5,843,723 (Dubensky et al.) OR (2) U.S. 5,843,723 (Dubensky et al.) in view of U.S. 5,951,975 (Falo et al.) in view of WO 95/32733 (Johnston 1) and US 5,792,462 (Johnston 2). As an initial point, Applicants respectfully note that they have already overcome a very similar rejection under 35 U.S.C. § 103(a) over Johnston 1 in view of Falo et al. Further, the present Office Action is the fourth Office Action on the merits and represents the third new set of rejections the Applicants have addressed. Applicants respectfully request full consideration of the arguments presented herein as well as previous arguments regarding Johnston 1 and Falo et al. so as to bring the lengthy prosecution of this application to a close.

The new rejection over Dubensky et al. in combination with the secondary references as well as the rejection over Johnston 1 in view of the secondary references will be addressed below.

Johnston 1 or Dubensky et al. are cited as the primary references. As noted by the Examiner and as previously remarked by the Applicants, Johnston 1 does not disclose the use of alphavirus vectors to deliver a cancer antigen. Moreover, neither the Johnston 1 nor Dubensky et al. reference is sufficient to establish a *prima facie* case of obviousness. Given the unpredictability in the art of cancer vaccines at the time of invention and the known difficulty in the art in eliciting an immune response against cancer antigens, one of ordinary skill in the art at the time of invention could have had no reasonable expectation of success in using the presently claimed compositions to treat cancer based on Johnston 1 or Dubensky et al., alone or in the cited combination with the secondary references. The Court of Appeals for the Federal Circuit has held that "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). These criteria are not satisfied by the outstanding obviousness rejection. Accordingly, the rejection should be withdrawn.

Falo et al. is applied as teaching "a method wherein the subject's immune system is being sensitized to an antigen that is expressed on cancer cells in the subject." (Office Action, page 10, first full paragraph). The Examiner concedes that "Falo does not teach the use of a viral vector to introduce the antigens", but argues that "it would have been obvious to one of ordinary skill in the art to use the antigens of Falo in the viral vectors of either Johnston or of Dubensky in view of Johnston 2." The Examiner further argues that "one of ordinary skill in the art would have had a reasonable expectation of success because Falo shows that the antigens were effective in eliciting an immune response." Applicants respectfully disagree. Both of these arguments are merely conclusory statements that are not supported by the references themselves. Further, Falo et al. does not teach an immunogenic composition expressing a cancer antigen for treating a subject having a cancer, or at risk of developing a

cancer, which expresses that same antigen or an antigenically-related molecule. As the Examiner concedes on page 11 (lines 4-5), Falo et al. only teaches the use of artifical antigens (which the Examiner refers to as "foreign"). Falo et al. does not suggest, and actually teaches away from, a viral composition expressing a cancer antigen that may be used to treat or prevent a cancer expressing that same antigen or an antigenically related molecule (*i.e.*, does not teach a viral composition expressing a self antigen).

Further, the results in the Olmsted Declaration, the Supplemental Olmsted Declaration, and the Long et al. poster/abstract clearly provide evidence of unexpectedly superior properties of the presently claimed invention as a cancer immunotherapy. The Office Action addresses Applicants' previous statements regarding unexpected results in the paragraph spanning pages 11-12 of the Office Action. Applicants respectfully note that they have previously overcome the teachings of Johnston 1 in view of Falo et al. as applied in the present rejection.

Applicants do not fully understand the statements in the Office Action regarding Dubensky et al., Johnston 1 and Falo et al. in connection with Applicants' unexpected results, but will make every effort to address the Examiner's concerns. The claimed compositions have clearly been demonstrated to be effective in inducing a protective immune response against a cancer antigen, even a cancer antigen that would be recognized as "self". If, for the sake of argument, Applicants adopt the Examiner's position that Falo et al. suggests the use of a cancer antigen as an artificial antigen, the Examiner has conceded that Falo et al. only suggests use of this antigen as a foreign antigen. Falo et al. does NOT suggest use of the cancer antigen to induce an immune response against a cancer that expresses that SAME antigen or an antigenically similar molecule (*i.e.*, does not teach vaccination with a self antigen). Instead, Falo et al. would be using the cancer antigen as any other artificial antigen, such as ovalbumin, to "cross prime" the immune system and produce an immune response against a different cancer antigen, which would be a self antigen.

Thus, the presently claimed compositions have **unexp ct d** and **superior** properties in that they are effective to **overcome tolerance** and induce a protective immune response against a cancer antigen that would be recognized as self. **The unexpected and superior properties of the claimed composition MUST be considered when assessing the nonobviousness thereof.** *In re Papesch,* 137 USPQ 43 (CCPA 1963). *In re Papesch* has already been extensively discussed in Applicants' response of September 28, 2001, which discussion was sufficient to overcome the previous rejection over Johnston 1 in view of Falo et al.

The Office Action states that "the fact that the claimed viral vaccine may be used in a single step method, while the cellular composition of Falo requires two steps is irrelevant as the antigen of Falo would have been inserted into the viral vectors of the other references, and would therefore have been used according to the methods of Johnston and Dubensky." (Office Action, page 12, lines 3-6). Applicants respectfully disagree. Neither Johnston 1, Dubensky et al., nor Falo et al. suggests that an alphaviral composition expressing a native cancer antigen can induce a protective immune response against the native cancer antigen or an antigenically-related molecule. Thus, Falo et al. cannot be combined with Johnston 1 and/or Dubensky et al. to arrive at the claimed invention.

The results provided in the two Olmsted Declarations and the Long abstract/poster represent an important breakthrough in the field of cancer immunotherapy. The claimed compositions possess properties that are unexpectedly superior to what one of ordinary skill in the art would have expected from a reading of the cited combination of Johnston 1, Dubensky et al., and Falo et al., and are therefore nonobvious over the disclosures of these references.

In view of the foregoing discussion, Applicants assert that the outstanding obviousness rejection cannot be maintained, and respectfully request withdrawal thereof.

IX. Conclusions.

The points and concerns raised by the Examiner in the outstanding Office Action having been addressed in full, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

Karen A. Magri
Registration No. 41,965

cc: Long et al. Abstract/Poster

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Karen Magri

Version with Markings to Sh w Changes Made

Please amend the claims as follows:

84. (Amended four times) A composition comprising infectious alphavirus particles in an immunogenically effective amount to prevent or treat cancer, wherein said alphavirus particles comprise one or more heterologous nucleotide sequences encoding a native cancer cell [an] antigen; and wherein said alphavirus particles infect antigen-presenting cells [and wherein said antigen is a native cancer cell antigen], and further wherein said alphavirus particles comprise one or more attenuating mutations [, said composition effective to treat a cancer cell expressing said native cancer antigen].

95. (Amended three times) A composition comprising infectious Venezuelan Equine Encephalitis (VEE) particles in an [amount effective to] immunogenically effective amount to prevent or treat cancer, wherein said VEE particles comprise one or more heterologous nucleotide sequences encoding a native cancer cell [an] antigen; and wherein said VEE particles infect antigen-presenting cells [and wherein said antigen is a native cancer cell antigen], and further wherein said VEE particles comprise one or more attenuating mutations[, said composition effective to treat a cancer cell expressing said native cancer antigen].

103. (Amended) A composition comprising infectious alphavirus particles in an amount effective to provide a protective immune response, wherein said alphavirus particles comprise one or more heterologous nucleotide sequences encoding a Her2 gene product [native cancer cell antigen; and wherein said native cancer cell antigen is a Her2/*neu* gene product], and wherein said alphavirus particles infect antigen-presenting cells, and further wherein said alphavirus particles comprise one or more attenuating mutations.

104. (Amended) A composition comprising infectious Venezuelan Equine Encephalitis (VEE) particles in an amount effective to provide a protective immune response, wherein said VEE particles comprise one or more heterologous nucleotide sequences encoding a Her2 gene product [native cancer cell antigen; and wherein said native cancer cell antigen is a Her2/*neu* gene product], and wherein said alphavirus particles infect antigen-presenting cells, and further wherein said VEE particles comprise one or more attenuating mutations.

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